Therapeutic Drug Monitoring to Guide Clinical Decision Making in Inflammatory Bowel Disease Patients with Loss of Response to Anti-TNF: A Delphi Technique-Based Consensus

Greuter, Thomas ; Maillard, Michel H ; Juillerat, Pascal ; Michetti, Pierre ; Seibold, Frank ; Mottet, Christian ; Zahnd, Nadine ; Sauter, Bernhard ; Schoepfer, Alain M ; Rogler, Gerhard ; Vavricka, Stephan R

Abstract: BACKGROUND Loss of response is frequently encountered in patients with inflammatory bowel disease (IBD) treated with antitumor necrosis factor (TNF) agents. Therapeutic drug monitoring (TDM) and antidrug antibody measurement are increasingly used in this setting. METHODS To establish a consensus on the use of TDM in the context of loss of response to anti-TNFs, we performed a vote using a Delphi-style process followed by an expert panel discussion among 8 IBD specialists practicing in Switzerland, Europe. Statements were rated on an even Likert-scale ranging from 1 (strong disagreement) to 4 (strong agreement), based on expert opinion and the available literature. RESULTS The experts agreed on the following statements: (i) loss of response is associated with inadequate drug levels in both Crohn's disease and ulcerative colitis; (ii) best timepoint for measuring drug levels is prior to the next application (= trough levels) with different thresholds for anti-TNF agents (infliximab 5 g/mL, adalimumab 8 g/mL, certolizumab pegol 10 g/mL); (iii) antidrug antibodies are predictive for loss of response; and (iv) antidrug-antibody titers and drug trough levels are key determinants in the treatment algorithm. Data about non-anti-TNF biologics were considered too limited to propose recommendations. CONCLUSION A Delphi-style consensus among 8 IBD experts shows that TDM and measurement of antidrug-antibody titers are useful in the context of loss of response to anti-TNF. Optimal cutoff levels depend on the type of anti-TNF. These values are critical in the decision making process. More studies are needed to address the value of such measurements for non-anti-TNF biologics.

DOI: https://doi.org/10.1159/000501930

THERAPEUTIC DRUG MONITORING TO GUIDE CLINICAL DECISION MAKING IN IBD PATIENTS WITH LOSS OF RESPONSE TO ANTI-TNF: A DELPHI TECHNIQUE-BASED CONSENSUS

Re-Submission to Digestion

Thomas Greuter MD[1]*, Michel H. Maillard MD PhD[2,3]*, Pascal Juillerat MD MSc[4], Pierre Michetti MD[3], Frank Seibold MD[5], Christian Mottet MD PhD[6], Nadine Zahnd PhD[7], Bernhard Sauter MD[8], Alain M. Schoepfer MD[2], Gerhard Rogler MD PhD[1], Stephan R. Vavricka MD[1,9]; on behalf of the Swiss IBDnet

[1]Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland
[2]Service of Gastroenterology and Hepatology, Lausanne University Hospital, Switzerland
[3]Crohn and Colitis Center, Gastroentérologie Beaulieu SA, Lausanne, Switzerland
[4]Gastroenterology, Clinic for Visceral Surgery and Medicine, Inselspital, University Hospital of Bern, Switzerland
[5]Crohn-Colitis Zentrum, Hochhaus Lindenhofspital, Bern, Switzerland
[6]Division of Gastroenterology, Hopital de Sion, Sion, Switzerland
[7]IBDnet, Zurich, Switzerland
[8]Gastrozentrum Hirslanden, Hirslanden Private Clinic Group, Zurich, Switzerland
[9]Zentrum für Gastroenterologie und Hepatologie, Zurich, Switzerland

*these authors contributed equally to this work

Address for Correspondence:
Prof. Dr. med. Stephan R. Vavricka
Zentrum für Gastroenterologie und Hepatologie
Vulkanplatz 8
CH-8048 Zürich
e-mail: vavricka@zgh.ch

Running title: *TDM in IBD*

CONFLICT OF INTEREST

Guarantors of the article: Thomas Greuter MD and Stephan R. Vavricka MD

Specific author contributions: Study design: GR, NZ and SRV; Literature research: TG, AMS and SRV; Acquisition and interpretation of data; TG, PJ, PM, FS, CM, BS, MM, GR and SRV; Drafting of manuscript: TG, MM and SRV; Expert panel discussion for the Delphi-like process: PJ, PM, FS, CM, BS, MM, GR and SRV. Critical review of the manuscript: PJ, PM, FS, CM, NZ, BS, MM, AMS and GR. Supervision: TG, MM, GR and SRV. All authors contributed to the critical revision and approved the final version of manuscript.

Potential competing interests: TG is a consultant for Sanofi Aventis, received a travel grant from Falk Pharma GmbH and Vifor, and an unrestricted research grant from Novartis. SRV received consultant fees and unrestricted research grants from Vifor, Sanofi Aventis and Falk Pharma GmbH. PM received consulting fees from AbbVie, Calypso, Ferring Pharmaceuticals, Merck Serono, MSD, Nestlé Health Sciences, Pfizer, Takeda, UCB Pharma, and Vifor Pharma, lecture fees from AbbVie, Ferring Pharmaceuticals, Hospira, MSD, Takeda, UCB Pharma, and Vifor Pharma and research grants from MSD, Takeda, and UCB Pharma. GR has consulted to Abbvie, Augurix, BMS, Boehringer, Calypso, Celgene, FALK, Ferring, Fisher, Genentech, Gilead, Janssen, MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions and Zeller; has received speaker's honoraria from Astra Zeneca, Abbvie, FALK, Janssen, MSD, Pfizer, Phadia, Takeda, Tillots, UCB, Vifor and Zeller; and has received educational grants and research grants from Abbvie, Ardeypharm, Augurix, Calypso, FALK, Flamentera, MSD, Novartis, Pfizer, Roche, Takeda, Tillots, UCB and Zeller. MHM received consultant fees from Abbvie, Calypso, Ferring, MSD, Pfizer, Takeda and Vifor as well as unrestricted grants from Vifor, UCB and Takeda. The other authors report no conflict of interest. No company representative was involved in conception, writing, or financing of this study

ABSTRACT

Background: Loss of response is frequently encountered in patients with inflammatory bowel disease (IBD) treated with anti-TNF agents. Therapeutic drug monitoring (TDM) and anti-drug antibody measurement are increasingly used in this setting.

Methods: To establish a consensus on the use of TDM in the context of loss of response to anti-TNFs, we performed a vote using a Delphi-style process followed by an expert panel discussion among eight IBD specialists practicing in Switzerland, Europe. Statements were rated on an even Likert-scale ranging from 1 (strong disagreement) to 4 (strong agreement), based on expert opinion and the available literature.

Results: The experts agreed on the following statements: i) Loss of response is associated with inadequate drug levels in both CD and UC; ii) Best time-point for measuring drug levels is prior to the next application (=trough levels) with different thresholds for anti-TNF agents (infliximab 5ug/mL, adalimumab 8ug/mL, certolizumab pegol 10ug/mL); iii) Anti-drug antibodies are predictive for loss of response; and iv) Anti-drug-antibody titers and drug trough levels are key determinants in the treatment algorithm. Data about non-anti-TNF biologics were considered too limited to propose recommendations.

Conclusion: A Delphi-style consensus among eight IBD experts shows that TDM and measurement of anti-drug-antibody titers are useful in the context of loss of response to anti-TNF. Optimal cut-off levels depend on the type of anti-TNF. These values are critical in the decision making process. More studies are needed to address the value of such measurements for non-anti-TNF biologics.

Word count: 238 words (word limit 250 words)

KEY WORDS: *Therapeutic drug monitoring, TDM, anti-drug-antibodies, inflammatory bowel disease, loss of response, consensus, anti-TNF*

INTRODUCTION

Inflammatory bowel disease (IBD) with its two subtypes Crohn's disease (CD) and ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract.(1) Given a complex and yet only partially understood etiopathogenesis, IBD is considered an incurable, but treatable disease.(2, 3) The introduction of anti-tumor-necrosis-factor (TNF) with considerable higher efficacy than conventional immunomodulatory drugs has dramatically changed the therapeutic management of IBD. However, loss of response is encountered in up to 46% of IBD patients treated with anti-TNF.(4, 5) Loss of response implies a previous initial response to treatment, which is lost over time, and has to be differentiated from primary non-response, where such response is never achieved.(4) To undermine this difference, loss of response is sometimes referred to as secondary non-response. Based on the mechanisms involved, loss of response can be either classified as immune-mediated (formation of antibodies against anti-TNF) or non-immune mediated (accelerated drug clearance due to burden of disease, weight or male gender, non-adherence, fibrostenotic disease phenotype).(4) Therapeutic drug monitoring (TDM) and anti-drug antibody measurement are increasingly used in the setting of a loss of response and data supporting their application in daily practice are emerging.(6-8) However – despite acknowledging the usefulness of TDM – current guidelines of the European Crohn`s and Colitis Organisation (ECCO) lack of a clear recommendation regarding optimal time-point, adequate thresholds and TDM`s exact role in the long-term therapeutic algorithm.(9, 10)

Therefore, we performed an expert panel discussion to reach a consensus statement based on the available literature about TDM. The goal of this discussion was to elaborate an algorithm for TDM in the context of biological therapy in IBD and a loss of response to such treatment. During an expert meeting, the relevance of thresholds and cut-off values for adequate drug concentrations and anti-drug-antibody titers were discussed and a therapeutic decision pathway was elaborated. The discussion focused on TDM for loss of response only, so therapy monitoring *per se* was not within the scope of the panel discussion. With this consensus study, we sought to answer the following questions: *1) When and why to measure and how to interpret drug levels? 2) When and why to measure and how to interpret anti-drug antibody titers?* And finally *3) what is the best treatment algorithm in case of a loss of response to anti-TNF?*

LITERATURE REVIEW

Definition of loss of response

There is no universally accepted definition of loss of response to anti-TNF treatment and hence its reported frequency is highly variable. Definitions used in clinical trials, observational studies and reviews are: 1) Re-emergence of clinical symptoms after induction of response, verified by an increase in clinical activity scores such as the Crohn`s disease activity index (CDAI, e.g. 70 point change) or Mayo score (e.g. 3 point change);(11, 12) 2) Patient`s perspective of increasing symptoms;(13) and 3) Need for dose intensification or treatment discontinuation with a switch to other agents.(5, 14, 15) Current ECCO guidelines suggest the following two possible definitions for loss of response in CD – acknowledging that no consensus exists: For CD 1) a CDAI>150 with an increase of more than 70 points or 2) a CDAI increase of ≥100 points;(9) For UC, ECCO did not release a statement regarding the definition of loss of response.(10) However, a Mayo score of >2 or an increase of 3 or more points might be used in daily clinical practice.(16, 17)

Drug levels and loss of response

Several studies demonstrated higher efficacy of anti-TNFs with higher serum drug levels, both in UC and CD, as well as for infliximab and other anti-TNF agents. Most data derive from retrospective analyses of prospective trials, which have been nicely summarized in a comprehensive review by Sorrentino *et al.*(18) In CD, high or detectable infliximab trough levels were associated with higher rates of ongoing clinical response compared to low or undetectable levels. These rates were: 1) 82 vs. 6% (for detectable vs. non-detectable);(19) 2) 74 vs. 59% (for cut off >3ug/ml);(20) 3) 39 vs. 18% (for cut off ≥3.5ug/mL);(21) 4) 92 vs. 14% (for cut off >0.3ug/mL);(22) and 5) 100 vs. 80% (for cut off >5ug/mL).(22) Moreover, there was a 66% lower likelihood to lose clinical response in case of drug concentrations above 3ug/mL.(23) Clinical remission rates increased after dose escalation to reach target levels of 3-7ug/mL (from 65 to 88%).(24) There was a longer duration of clinical response in patients with a threshold of >12ug/mL.(25) In addition, higher rates of endoscopic remission (47 vs. 19%) were observed with detectable infliximab levels (vs. non-detectable).(19) In UC, detectable infliximab levels were also associated with higher clinical (69 vs. 15%) and endoscopic (76 vs. 28%) response rates.(26) Patients in endoscopic remission had higher levels of infliximab (8.1 vs. 2.9), and an infliximab threshold level of >6.6mug/mL predicted

endoscopic response with an odds ratio of 18.1.(27) In both UC and CD, loss of response to infliximab was attributed to low drug levels in 45%.(28)

Fewer studies have been performed with adalimumab. In CD, trough levels of ≥5ug/ml have been identified as predictive for treatment continuity with an odds ratio of 4.5.(29) Higher trough levels were further observed with clinical remission and mucosal healing.(30) In UC, patients with histological and endoscopic inflammation had lower drug levels, while those in clinical remission and with mucosal healing showed higher serum concentrations of adalimumab.(31) A comprehensive analysis of 145 patients examined the impact of adalimumab and infliximab drug levels in both UC and CD.(32) The following rates of mucosal healing were found: 1) with infliximab 50% for >4ug/mL, 85% for >6ug/mL and 90% for >8ug/mL; and 2) with adalimumab 50% for >7.5ug/mL, 75% for >8ug/mL and 90% for >12ug/mL.(32) A plateau was reached with >12ug/ml (adalimumab) and >8ug/ml (infliximab). For certolizumab, even fewer data are available: With higher drug levels (≥23.30 vs <8.98ug/mL), more CD patients were found to be in clinical remission (93 vs. 50%), endoscopic remission (75% vs. 30%) and to show endoscopic response (87.5 vs. 20%).(33)

Despite these positive data – however – in some trials no association between drug levels and treatment outcome was seen: in the SONIC trial, no significant differences were observed in terms of remission rates at week 50 when patients with non-detectable infliximab levels (0ug/mL) were compared with patients with higher drug levels (>6ug/mL, 67% vs. 87%).(18, 20) Similar findings were reported by Pariente and colleagues.(34) In addition, optimal cut-off values remain unclear. This is mainly attributed to the fact that many different thresholds have been used in the so far conducted trials, ranging from >1 to >12ug/mL in case of infliximab. Different outcomes were used to define therapeutic response ranging from clinical response, remission to endoscopic response, remission. Since most data evolve from retrospective analyses of prospective studies, the evidence for TDM is low. The value of pro-active drug level measurements and targeting infliximab treatment to a pre-defined serum concentration (target: 3-7ug/mL) was evaluated in the TAXIT trial: While indeed clinical remission rates increased with dose escalation in patients with subtherapeutic drug levels, this strategy was not superior to clinically based dosing.(24) Similarly, maintaining infliximab above 3ug/mL did not result in higher rates of steroid-free clinical remission than adapting dose based only on symptoms (TAILORIX trial).(35) Taken together, no clear recommendations for the use of TDM and for optimal thresholds in particular exist.(7) Suggested cut-offs vary

from >2ug/mL to 5-10ug/mL. Current recommendations regarding the use of TDM and adequate threshold levels in IBD patients are summarized in **Table 1**.(9, 10, 36-40)

Anti-drug-antibodies

Development of anti-drug-antibodies, a process called anti-TNF immunogenicity, may also affect the efficacy of anti-TNF treatment. Anti-drug-antibody formation has been observed with all anti-TNF agents used in IBD. Of note, episodic dosing resulted in higher antibody titers than did scheduled dosing.(25, 41-45) Anti-drug-antibodies have been linked to higher rates of loss of response and higher likelihood of transfusion reactions.(25, 42, 43) Anti-drug-antibody titers can be measured with commercially available tests, which are based on ELISA, RIA or HMSA methods.(6, 41, 46) Data on the association between presence of anti-drug-antibodies and disease outcome are inconsistent.(41) In CD studies with episodic dosing of infliximab, higher antibody titers were linked to shorter duration of response and lower response rates, while no such association was seen with scheduled dosing except for the SONIC trial, where some improvement was observed with inconclusive anti-drug-antibody titers.(19, 20, 25, 42-44) In UC, even higher response rates were seen with detectable antibodies, which was probably confounded by higher trough levels in these patients.(47) No such association was found in the study by Seow et al.(26) For adalimumab and certolizumab, no associations between anti-drug-antibodies and disease outcome were seen.(14, 48, 49) Detailed descriptions of these trials can be found in the thorough reviews by Scott and Lichtenstein, and by Khanna and colleagues.(6, 41) No clear cut-offs for anti-drug-antibodies exist due to different measurement methods and the fact that anti-drug-antibodies may be only transient in a considerable proportion of patients. While some studies used absence vs. presence of antibodies, others used defined threshold values. There are no clear recommendations regarding the use of anti-drug-antibodies in IBD treatment. In addition, there is no consensus regarding adequate threshold values (**Table 1**). However, anti-drug-antibody titers may have their value in clinical practice. A study from the Mayo Clinic revealed higher response rates for switch of anti-TNF agent compared to dose intensification in case of presence of anti-drug-antibodies (92 vs. 17%), while dose intensification was more effective if no anti-drug-antibodies were present (86 vs. 33% compared to switch of anti-TNF agent).(28) Similarly, Roblin and colleagues demonstrated high clinical response rates (67%) with adalimumab dose optimization in case of low trough levels and non-detectable anti-drug-antibodies.(50) In addition, combined interval shortening and dose intensification appears to

be particularly effective for restoring therapeutic drug levels when anti-drug-antibodies titers are low.(51) Nonetheless, dose intensifications can still be effective even in case of high anti-drug-antibody titers (in 60% compared to 74% efficacy in patients with non-detectable anti-drug-antibodies).(34)

METHODS

Delphi-style consensus

To establish a consensus on the use of TDM in the context of loss of response to anti-TNF treatment, we performed a vote among IBD experts using a Delphi-style process.(52) First, we conducted a literature review using PubMed and Embase. The following key search items were used: *loss of response, TDM, anti-TNF, anti-drug-antibodies, and inflammatory bowel disease.* In addition, guidelines from five gastroenterology societies were consulted: American Gastroenterology Association (AGA), American College of Gastroenterology (ACG), European Crohn`s and Colitis Organisation (ECCO), Asian Pacific Association of Gastroenterology (APAGE) and World Gastroenterology Organisation (WGO). In a second step, eight IBD specialists participated in a three-hour meeting and rated different statements on an even Likert-scale ranging from 1 to 4, based on their expert opinion and the available literature: 1 indicated strong disagreement with a specific statement, 2 disagreement, 3 agreement, and 4 indicated strong agreement. The statements included i) reason for and optimal time-point of TDM; ii) use of anti-drug-antibodies; iii) definition of loss of response; and iv) most adequate treatment strategies in case of loss of response to anti-TNF. A list of the statements used for the first round of voting can be found in **Supplementary Table 1**. Participants were blinded to the votes of the other IBD experts. The voting process was followed by a panel discussion to refine the statements. A statement was considered accepted if the mean rating value was 3 or more. As data are limited for biologics beyond the anti-TNF mode of action, statements were restricted to anti-TNF treatment. The eight IBD experts were as follows: five experts practice in and/or are affiliated with an academic institution (university hospital level), two experts practice in private practice and one expert practices at a large community hospital (all in Switzerland, Europe).

Ethical statement

This study did not include patient subjects. Therefore, as for other Delphi-technique based consensus paper, ethical approval was not required.(53)

RESULTS

TDM for anti-TNF

After the specialist panel opinion, the following consensus on therapeutic drug levels was achieved: 1) Loss of response is associated with low or undetectable serum drug concentration in 50-70% of cases (mean value 3.4, **Supplementary Figure 1**), and 2) both in CD and UC, loss of response is associated with low or undetectable serum drug levels (mean value 3.6, **Supplementary Figure 1**). There was a consensus on how anti-TNF clearance occurs: through immune-mediated reactions (with formation of anti-drug-antibodies, mean value 3.6) and non-immune reactions (mean value 3.6, **Supplementary Figure 1**). There was strong agreement that non-immune-mediated drug clearance is affected by severity and extent of IBD (mean value 3.9), male sex (mean value 3.3), BMI (mean value 3.5) and concomitant use of immunomodulators (mean value 3.8, **Supplementary Figure 2**). There was also strong consensus on when to measure drug concentrations in terms of infliximab (trough levels immediately before the administration of the next dose, mean value 4). However, there was no consensus regarding when to measure drug concentrations of subcutaneously administered anti-TNF. In terms of adequate anti-TNF levels, there was strong agreement that mucosal healing should be the target to treat. Optimal cut-off values to achieve this goal were controversially discussed (**Supplementary Figure 3**). However, there was a final agreement for infliximab (5ug/mL), adalimumab (8ug/mL) and certolizumab pegol (10ug/mL, **Figure 1**). There was no agreement regarding an optimal threshold for golimumab.

Anti-drug antibodies

In a next step, use of and cut-off values for anti-drug-antibodies were rated and discussed. There was overall agreement that high anti-drug-antibody titers are predictive for adverse events and loss of response, but that they do not predict mucosal healing, CRP levels or calprotectin levels (**Supplementary Figures 4**). There was consensus to use manufacturer`s cut-off values for anti-infliximab and adalimumab antibody titers. The test provider usually indicates if levels are considered positive or negative. All positive levels are meaningful. In addition, there was an overall agreement that anti-drug-antibodies should be measured when drug levels are lowest to avoid the risk of complex formation. There was no consensus on specific cut-off values for certolizumab pegol and golimumab. The value of anti-vedolizumab antibodies remains unclear – and was not within the scope of the current consensus.

Loss of response to anti-TNF

There was overall agreement on how to define loss of response. The following parameters should be considered: symptoms (mean value 3.4), drug levels (mean value 3.1), anti-drug-antibodies (mean value 3.1), and imaging such as sonography (mean value 3.1), endoscopy (mean value of 3.5) and MRI (in case of Crohn`s disease, mean value 3.1, **Supplementary Figure 5**). A calprotectin level of >50ug/g was not considered to affect clinical decision making (mean value 2.6). However, after discussing optimal cut-off levels, there was a strong agreement that calprotectin levels of >200ug/g should be taken into account, when defining loss of response.

Therapeutic algorithm for patients with loss of response to anti-TNF

The following interventions were deemed appropriate in the context of loss of response: 1) shortening of dose interval or dose intensification in case of subtherapeutic drug levels, and absent or low anti-drug-antibody titers; 2) switch to another anti-TNF (=switch in class) in case of subtherapeutic drug levels, but presence of anti-drug-antibodies; and 3) switch to a non-anti-TNF biologic (=switch out of class) in case of therapeutic drug levels regardless of presence or absence of anti-drug-antibodies. In case of subtherapeutic drug levels, but absent or low anti-drug-antibody titers, two options were deemed appropriate: 1) increasing the dose ("dose intensification") or 2) shortening the interval. The experts agreed on the following: 1) dose intensification should be strived for if the clinical effect after drug administration is slow; and 2) shortening the interval should be favored if a patient still responds to a maintenance dose, but experiences deterioration of IBD symptoms prior to the next drug administration. **Figure 2** shows a treatment algorithm in case of loss of response to anti-TNF, which was elaborated during this expert panel discussion.

DISCUSSION

TDM and measurement of anti-drug-antibodies are increasingly used in the context of loss of response to anti-TNF. As of yet, ECCO guidelines mention these novel tools but without clear recommendations about their use.(9, 10) We herein report on the results from a Delphi-based consensus meeting among eight IBD specialists. The final statements are summarized in **Table 2**.

Our expert panel reached consensus that loss of response to anti-TNF is associated with inadequate anti-TNF drug levels in both CD and UC. Indeed, despite some negative data from the SONIC trial, most published analyses showed that higher trough levels lead to better clinical and endoscopic outcomes.(18, 20) Most data are available for infliximab, but similar results have been reported for other anti-TNF agents. There was consensus that drug levels should be measured, when concentration is lowest (=trough levels). However, optimal cut-off values were discussed controversially among the panel experts. Current data are limited by the fact that studies used many different thresholds to define adequate and non-adequate drug concentrations. Nonetheless, a second voting round resulted in a consensus for infliximab (5ug/mL), adalimumab (8ug/mL) and certolizumab pegol (10ug/mL). These cut-offs should be seen as guiding values. Such guidance may help clinicians to decide whether or not a current anti-TNF therapy is under-dosed. A limiting factor of the current recommendation is that it may take up to two weeks until anti-TNF drug levels are available. Thus, an intervention is often needed and performed before the results are known. Point-of-care measures of anti-TNF may allow clinicians to take more advantage of TDM in the future.

Available data for anti-drug-antibodies are less consistent than they are for drug concentrations.(41) However, our expert panel reached consensus that anti-drug-antibody titers are useful and high titers are associated with loss of response to anti-TNF. This agreement was achieved based on 1) data from the SONIC trial,(20) 2) a recent meta-analysis showing worse outcome with anti-drug-antibodies at least in CD,(54) 3) and the fact that – if anti-drug-antibodies are present – switch to another anti-TNF results in better clinical response than dose intensification.(28) Thus, anti-drug antibodies should be taken into consideration when it comes to define loss of response to anti-TNF. However, threshold values remain unknown. As of today, any positive result evolving from antibody testing (based on the manufacturer`s protocol) should be considered clinically meaningful.

Based on these data and agreements, both trough levels and anti-drug-antibody titers should be seen as key determinants in the treatment algorithm. After loss of response is confirmed, drug monitoring is recommended. If therapeutic drug levels are detected, anti-TNF dose intensification has no benefit. Treatment should be switched out of class, high dose steroids might be started or even surgery might be considered. In case of inadequate drug levels, anti-drug antibody titers may help in clinical decision making: 1) undetectable antibody or low antibody titers justify dose intensification, while 2) high anti-drug-antibody titers should lead to a therapeutic switch out of class or maybe within class, but with optimization of concomitant immunomodulation. Some anti-TNF have lower immunogenic potential than others (e.g. adalimumab).(55) This strategy is mainly based on the retrospective analysis from Mayo Clinic, where in patients with low drug levels dose intensification was superior to anti-TNF switching, but in patients with anti-drug-antibodies, switching to other agents was superior to dose escalation.(28) In another study – however – dose intensification was effective even in patients with high anti-drug-antibody titers.(34)

Our consensus recommendations have several limitations. They only discuss anti-TNF treatment, since conclusive data are still missing for the newer non-anti-TNF biologics. Measuring vedolizumab levels is complicated because of saturation of the target receptor. In addition, patients may be in clinical remission despite undetectable or very low vedolizumab levels. Ustekinumab trough levels can now be measured. However, data supporting their use in clinical practice are too sparse.(7) The literature review was not conducted in the sense of a systematic review, but rather based on recent meta-analyses, reviews, guidelines, and studies in high impact journals. A further limitation of our consensus is that there is still no generally accepted definition for loss of response to anti-TNF. Therefore, the therapeutic algorithm provided in **Figure 6** should be seen as guidance rather than a rule for every patient. Clinical decision making should be discussed on individual basis.

In conclusion, a Delphi-style consensus among eight IBD experts shows that TDM and measurement of anti-drug-antibody titers are useful in the context of loss of response to anti-TNF. Optimal cut-off levels depend on the type of anti-TNF. These values are critical in the decision making process. More studies are needed to address the value of such measurements for non-anti-TNF biologics.

TABLES AND FIGURES

REFERENCES

1. Vavricka SR, Gubler M, Gantenbein C, Spoerri M, Froehlich F, Seibold F, et al. Anti-TNF Treatment for Extraintestinal Manifestations of Inflammatory Bowel Disease in the Swiss IBD Cohort Study. Inflamm Bowel Dis. 2017.
2. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annu Rev Immunol. 2010;28:573-621.
3. Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal Manifestations of Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015;21(8):1982-92.
4. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther. 2011;33(9):987-95.
5. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol. 2009;104(3):760-7.
6. Khanna R, Sattin BD, Afif W, Benchimol EI, Bernard EJ, Bitton A, et al. Review article: a clinician's guide for therapeutic drug monitoring of infliximab in inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(5):447-59.
7. Heron V, Afif W. Update on Therapeutic Drug Monitoring in Crohn's Disease. Gastroenterol Clin North Am. 2017;46(3):645-59.
8. Kopylov U, Seidman E. Predicting durable response or resistance to antitumor necrosis factor therapy in inflammatory bowel disease. Therap Adv Gastroenterol. 2016;9(4):513-26.
9. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. 2017;11(1):3-25.
10. Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. J Crohns Colitis. 2017;11(7):769-84.
11. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007;132(3):863-73; quiz 1165-6.
12. Allez M, Karmiris K, Louis E, Van Assche G, Ben-Horin S, Klein A, et al. Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. J Crohns Colitis. 2010;4(4):355-66.
13. Regueiro M, Siemanowski B, Kip KE, Plevy S. Infliximab dose intensification in Crohn's disease. Inflamm Bowel Dis. 2007;13(9):1093-9.
14. Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology. 2009;137(5):1628-40.
15. de Ridder L, Rings EH, Damen GM, Kneepkens CM, Schweizer JJ, Kokke FT, et al. Infliximab dependency in pediatric Crohn's disease: long-term follow-up of an unselected cohort. Inflamm Bowel Dis. 2008;14(3):353-8.
16. Higgins PD, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. Gut. 2005;54(6):782-8.
17. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65.e1-3.
18. Sorrentino D, Nguyen V, Henderson C, Bankole A. Therapeutic Drug Monitoring and Clinical Outcomes in Immune Mediated Diseases: The Missing Link. Inflamm Bowel Dis. 2016;22(10):2527-37.

19. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol. 2006;4(10):1248-54.
20. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383-95.
21. Cornillie F, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 2014;63(11):1721-7.
22. Drobne D, Bossuyt P, Breynaert C, Cattaert T, Vande Casteele N, Compernolle G, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2015;13(3):514-21.e4.
23. Bortlik M, Duricova D, Malickova K, Machkova N, Bouzkova E, Hrdlicka L, et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. J Crohns Colitis. 2013;7(9):736-43.
24. Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148(7):1320-9.e3.
25. Baert F, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003;348(7):601-8.
26. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut. 2010;59(1):49-54.
27. Brandse JF, Mathôt RA, van der Kleij D, Rispens T, Ashruf Y, Jansen JM, et al. Pharmacokinetic Features and Presence of Antidrug Antibodies Associate With Response to Infliximab Induction Therapy in Patients With Moderate to Severe Ulcerative Colitis. Clin Gastroenterol Hepatol. 2016;14(2):251-8.e1-2.
28. Afif W, Loftus EV, Faubion WA, Kane SV, Bruining DH, Hanson KA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol. 2010;105(5):1133-9.
29. Baert F, Kondragunta V, Lockton S, Vande Casteele N, Hauenstein S, Singh S, et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. Gut. 2016;65(7):1126-31.
30. Roblin X, Marotte H, Rinaudo M, Del Tedesco E, Moreau A, Phelip JM, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2014;12(1):80-4.e2.
31. Yarur AJ, Jain A, Hauenstein SI, Quintero MA, Barkin JS, Deshpande AR, et al. Higher Adalimumab Levels Are Associated with Histologic and Endoscopic Remission in Patients with Crohn's Disease and Ulcerative Colitis. Inflamm Bowel Dis. 2016;22(2):409-15.
32. Ungar B, Levy I, Yavne Y, Yavzori M, Picard O, Fudim E, et al. Optimizing Anti-TNF-α Therapy: Serum Levels of Infliximab and Adalimumab Are Associated With Mucosal Healing in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2016;14(4):550-7.e2.
33. Colombel JF, Sandborn WJ, Allez M, Dupas JL, Dewit O, D'Haens G, et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(3):423-31.e1.

34. Pariente B, Pineton de Chambrun G, Krzysiek R, Desroches M, Louis G, De Cassan C, et al. Trough levels and antibodies to infliximab may not predict response to intensification of infliximab therapy in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(7):1199-206.
35. D'Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. Gastroenterology. 2018;154(5):1343-51.e1.
36. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S, Committee AGAICG. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017;153(3):827-34.
37. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113(4):481-517.
38. Bernstein CN, Eliakim A, Fedail S, Fried M, Gearry R, Goh KL, et al. World Gastroenterology Organisation Global Guidelines Inflammatory Bowel Disease: Update August 2015. J Clin Gastroenterol. 2016;50(10):803-18.
39. Ooi CJ, Fock KM, Makharia GK, Goh KL, Ling KL, Hilmi I, et al. The Asia-Pacific consensus on ulcerative colitis. J Gastroenterol Hepatol. 2010;25(3):453-68.
40. Ooi CJ, Makharia GK, Hilmi I, Gibson PR, Fock KM, Ahuja V, et al. Asia-Pacific consensus statements on Crohn's disease. Part 2: Management. J Gastroenterol Hepatol. 2016;31(1):56-68.
41. Scott FI, Lichtenstein GR. Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease. Curr Treat Options Gastroenterol. 2014;12(1):59-75.
42. Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology. 2003;124(4):917-24.
43. Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut. 2007;56(9):1226-31.
44. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol. 2004;2(7):542-53.
45. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359(9317):1541-9.
46. Wang SL, Ohrmund L, Hauenstein S, Salbato J, Reddy R, Monk P, et al. Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum. J Immunol Methods. 2012;382(1-2):177-88.
47. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462-76.
48. Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen O, Hanauer SB, McColm J, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med. 2007;357(3):239-50.
49. Sandborn WJ, Abreu MT, D'Haens G, Colombel JF, Vermeire S, Mitchev K, et al. Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. Clin Gastroenterol Hepatol. 2010;8(8):688-95.e2.

50. Roblin X, Rinaudo M, Del Tedesco E, Phelip JM, Genin C, Peyrin-Biroulet L, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. Am J Gastroenterol. 2014;109(8):1250-6.
51. Dreesen E, Van Stappen T, Ballet V, Peeters M, Compernolle G, Tops S, et al. Anti-infliximab antibody concentrations can guide treatment intensification in patients with Crohn's disease who lose clinical response. Aliment Pharmacol Ther. 2018;47(3):346-55.
52. Prinsen CA, Vohra S, Rose MR, King-Jones S, Ishaque S, Bhaloo Z, et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. Trials. 2014;15:247.
53. Vuitton L, Peyrin-Biroulet L, Colombel JF, Pariente B, Pineton de Chambrun G, Walsh AJ, et al. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. Aliment Pharmacol Ther. 2017;45(6):801-13.
54. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. Am J Gastroenterol. 2013;108(1):40-7; quiz 8.
55. Chaparro M, Guerra I, Muñoz-Linares P, Gisbert JP. Systematic review: antibodies and anti-TNF-α levels in inflammatory bowel disease. Aliment Pharmacol Ther. 2012;35(9):971-86.

	ECCO	AGA	ACG	WGO	APAGE
Use of TDM	Could be used to guide optimisation strategy if available	Reactive TDM suggested to guide treatment changes if active anti-TNF treated IBD	Should be considered in active disease	More widely available for infliximab than any other anti-TNF. It can help determine the cause of a secondary loss of response and may be adopted in dose reduction strategies.	No Statement
Threshold for adequate drug levels	No statement	Infliximab ≥5ug/mL Adalimumab ≥7.5ug/mL Certolizumab ≥20ug/mL Golimumab unknown	infliximab > 7.5 ug/mL, adalimumab > 5ug/mL, and certolizumab pegol >20ug/mL	No Statement	No Statement
Use of anti-drug-antibodies	Could be used to guide optimisation strategy if available	No Statement	Should be considered in active disease	More widely available for infliximab than any other anti-TNF. It can help determine the cause of a secondary loss of response and may be adopted in dose reduction strategies.	No Statement
Cut-off values for anti-drug-antibodies	No Statement	No Statement	No Statement	No Statement	No Statement

Table 1: Current recommendations regarding drug levels and anti-drug-antibodies in inflammatory bowel disease. ACG, American College of Gastroenterology; AGA, American Gastroenterology Association; APAGE, Asian Pacific Association of Gastroenterology; ECCO, European Crohn`s and Colitis Organisation; WGO, World Gastroenterology Organisation

FINAL STATEMENTS
Loss of response is associated with inadequate drug levels in both CD and UC
Best time-point for measuring drug levels is prior to the next application (trough levels)
Thresholds for adequate drug levels depend on the anti-TNF agent.
Anti-drug-antibodies are predictive for loss of response and adverse events
Manufacturer's cut-off values for anti-drug antibodies should be used and all positive levels should be considered meaningful
Anti-drug-antibody titers and drug trough levels are key determinants in the treatment algorithm

Table 2: Overview of the final statements made during the expert panel discussion